IN-STENT RESTENOSIS
FROM A TO Z

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THIS EPISODE'S OVERVIEW

- Mechanism of ISR
- Pathophysiologic consideration
- Intravascular imaging findings
- Management of ISR
- DES ISR
- BMS ISR
- DCB role in ISR
- Future perspective

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INTRODUCTION

ISR is characterised by a significant reduction in the luminal diameter within the stented segment after a successful PCI and remains the ***most common cause of stent failure***

While the relative incidence of ISR has reduced with newer drug-eluting stent (DES) technologies in comparison to the bare metal stent (BMS) era treatment of ***ISR still accounts for 5-10%(US up to 10%, EU 5%)of all PCI procedures*** performed in clinical practice

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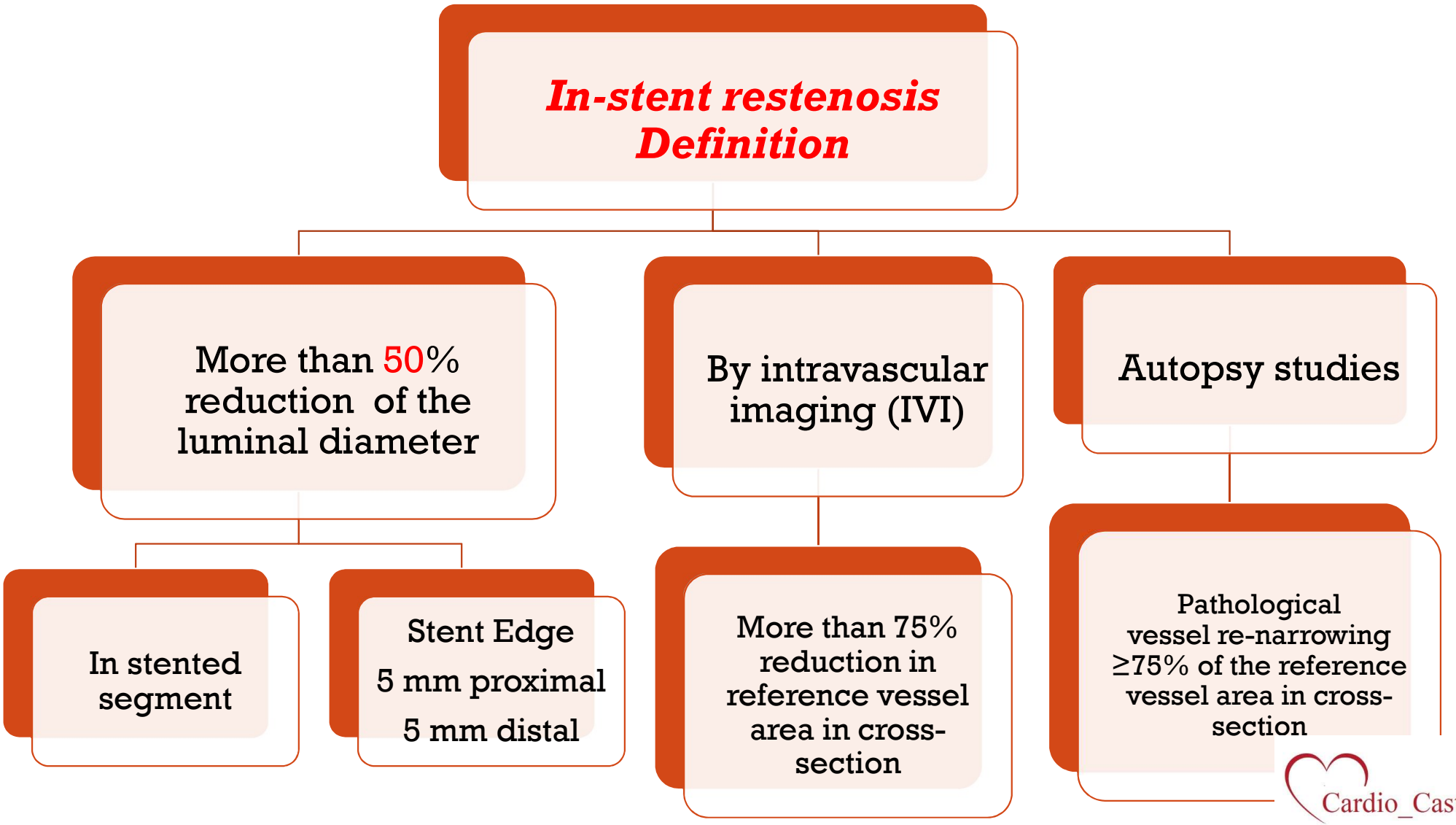
In-stent restenosis Definition
More than 50% reduction of the luminal diameter
By intravascular imaging (IVI)
Autopsy studies
In stented segment
Stent Edge
5 mm proximal
5 mm distal
More than 75% reduction in reference vessel area in cross-section
Pathological vessel re-narrowing ≥75% of the reference vessel area in cross-section
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The term ***"clinical restenosis"*** is sometimes used to refer to ISR associated with symptoms or signs of ischaemia. Given that not all ISR results in symptoms or signs of ischaemia (referred to as "silent restenosis"), rates of clinical restenosis are consequently lower than overall rates of ISR. Similarly to *de novo* coronary artery disease (CAD), percutaneous interventional treatment of ISR may be indicated for patients presenting with either

A-Acute coronary syndrome (ACS) or

B-Chronic coronary syndrome (CCS)

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ANGIOGRAPHIC CLASSIFICATION BY MEHRAN ET AL

In BMS-ISR

ISR length (≤10 mm: focal, >10 mm: diffuse)

ISR location (within or beyond stent borders)

Occlusion (yes or no)

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APPLICATION OF THIS CLASSIFICATION SYSTEM RESULTS IN FOUR MAIN GROUPS:

- Type I: focal
- Type II: diffuse, within stent
- Type III: diffuse, within and beyond stent
- Type IV: occlusive

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MECHANISMS OF ISR

Potential mechanical or technical factors associated with ISR include

- Stent Undersizing
- Stent Underexpansion
- Vessel Calcification
- Stent Fracture
- Geographic Missmatch

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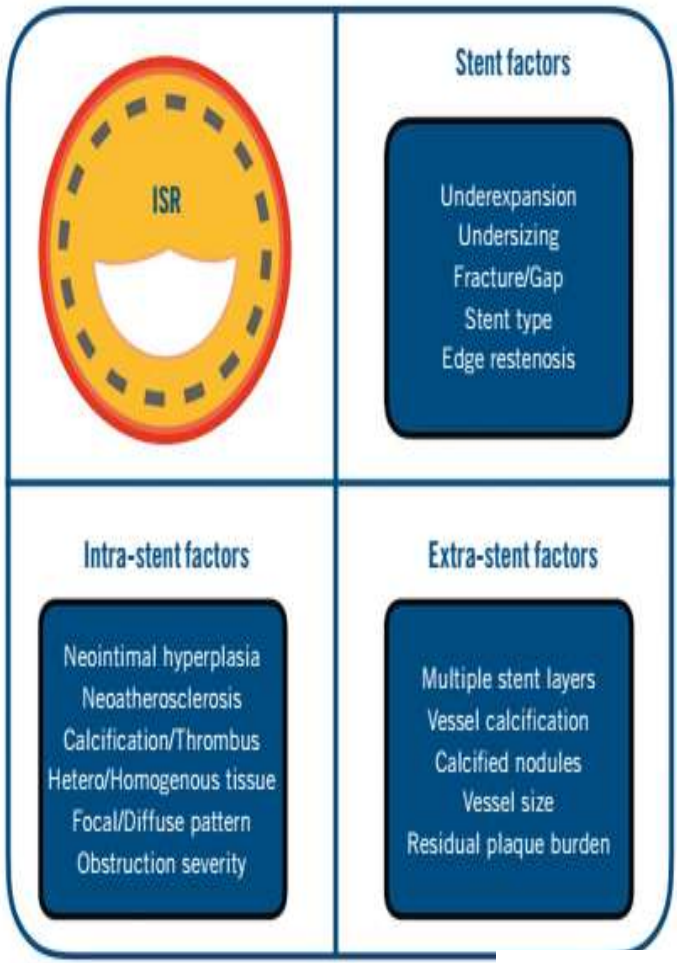
3 categories of factors may be attributed to a variable degree of influence ISR

Extra-stent factors(vessel calcification or multiple stent layers)

Stent-related factors (i.e., stent undersizing, stent fracture)

Intra-stent factors (i.e., excessive tissue proliferation within the stent)



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BIOLOGICAL MECHANISMS OF ISR

1- ***Neointimal Hyperplasia*** is defined as the accumulation of smooth muscle cells and extracellular matrix in the intima

2-***Neoatherosclerosis*** is characterised by an Accumulation of lipid-laden foamy macrophages, with or without necrotic core formation, and/or calcification within the neointima

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MECHANISMS OF ISR: BMS-ISR VS DES-ISR

Despite the obvious superficial commonalities, current evidence suggests that BMS-ISR and DES-ISR could be considered as distinct pathological entities

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Table 1. Comparison of the principal imaging and histological features of restenotic tissue after drug-eluting stent and bare metal stent implantation.

	Bare metal stent restenosis	Drug-eluting stent restenosis
Imaging features		
Angiographic morphology	Diffuse pattern more common	Focal pattern more common
OCT tissue properties	Homogenous, high signal band most common	Layered structure or heterogenous most common
Time course of late luminal loss	Late loss maximal by 6-8 months	Ongoing late loss out to 5 years
Histopathological features		
Smooth muscle cellularity	Rich	Hypocellular
Proteoglycan content	Moderate	High
Peri-strut fibrin and inflammation	Occasional	Frequent
Complete endothelialisation	3-6 months	Up to 48 months
Thrombus present	Occasional	Occasional
Neoatherosclerosis	Relatively infrequent, late	Relatively frequent, accelerated course

OCT: optical coherence tomography

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NEOATHEROSCLEROSIS

- Optical coherence tomography (OCT) findings suggestive of neoatherosclerosis
  Less common in DES-ISR within the first year post-PCI (early DES-ISR)
- More common in DES-ISR which develops after 1 year postPCI (late DES-ISR)
- Neoatherosclerosis demonstrates an accelerated course in comparison to *de novo* atherosclerotic

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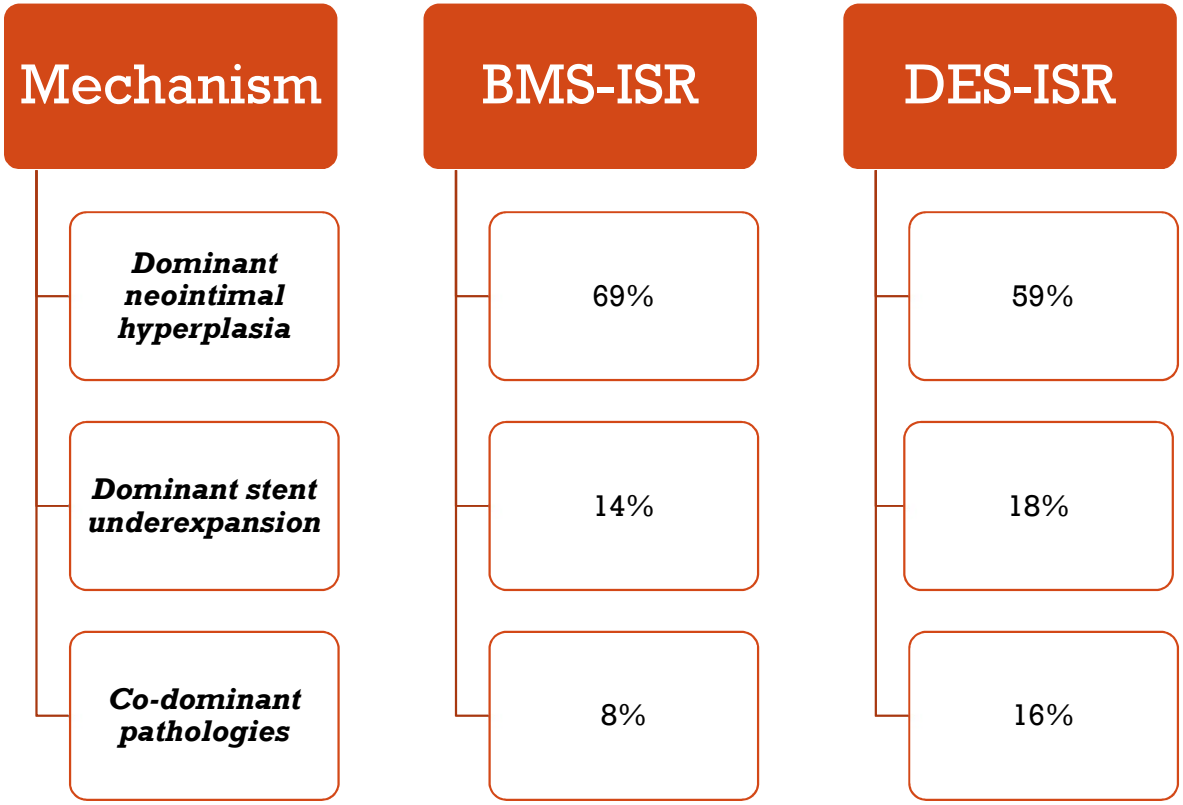
IVUS FINDING IN ISR



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In that study, a cut-off value of <5 mm2 stent cross-sectional area (CSA) at the minimal lumen area (MLA) site was used to define stent underexpansion

a value of 50% percentage neointimal hyperplasia at the MLA site was used to define dominant intimal hyperplasia.

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TIME COURSE OF ISR

BMS-ISR was recognised to peak within the ***first 6 months*** post-stent implantation

DES-ISR appears to continue to ***increase steadily for several years*** after stent implantation

Increased identification of ***"silent" ISR*** in patients who undergo routine angiographic surveillance

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CLINICAL PRESENTATION

ISR slowly progressive, relatively benign, pathological process.

It is now increasingly recognised that ISR is not benign and can commonly present as an ACS.

To have elevations in ***high-sensitivity troponin levels***, fulfilling the current criteria for ***spontaneous myocardial infarction***.

In patients with DES-ISR, IVI has demonstrated

A- Acute plaque rupture

B- Stent thrombosis (ST)

Higher risk of recurrent major adverse cardiovascular events (***MACE***) and angiographic restenosis after ISR-PCI

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IMAGING FOR ISR: STENT ENHANCEMENT

StentBoost also known as "stent enhancement" techniques, have also been reported to be useful for the detection of inadequate stent expansion, demonstrating superior correlations for stent expansion measured by IVUS when compared with quantitative coronary angiography.

Stent enhancement is quickly performed in the cath lab

Stent fracture

Stent underexpansion

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IMAGING FOR ISR: IVI

Guidelines: (Class IIa, Level B) the use of IVI in order to assess ISR.

Precise Underlying mechanisms and patterns of ISR and Treatment Option (through appropriate device and interventional strategy selection) with consequently improved outcomes.

No RCTs supporting the differential treatment of ISR based on IVI appearances.

In fact, there is a paucity of data on long-term outcomes following IVI-guided treatment of ISR and the majority of RCTs on the management of ISR did not mandate the use of IVI

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Heterogenous ISR on OCT DESs showed an advantage over DCBs. No such advantage was seen in patients with a homogenous pattern on OCT.

Indeed, this hypothesis will be examined by the ***upcoming ISAR-DESIRE 5 trial***, an RCT with a factorial design randomising patients with homogenous and heterogenous ISR tissue patterns on OCT to either DCB or DES treatment.

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OCT

Wavelength of 1.3 µm

Axial resolution of 12-15 µm

10 times the spatial resolution of IVUS

Uniquely detailed neointimal tissue characterization and the identification of neoatherosclerosis

However, limitations of OCT include the need to use contrast media to ensure a blood-free field for image acquisition, which may be difficult to achieve in

Tight Lesions

Ostial ISR lesions

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Moreover, due to reduced tissue penetration with OCT compared to IVUS the ***external elastic lamina (EEL)*** cannot always be adequately identified, which can lead to difficulties with vessel sizing.

This may be particularly ***challenging in patients with multiple metal stent layers.***

Although OCT requires the injection of higher volumes of contrast media, which may be proarrhythmogenic and increase the likelihood of post-procedural acute kidney injury, the occurrence of these complications is rare.

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BASED ON OCT APPEARANCES, ISR CAN BE CLASSIFIED INTO FOUR GROUPS:

Homogeneous: uniform high signal intensity, low back-scatter, typical of areas of high smooth muscle cell content

Heterogeneous: mixed signal intensity, may represent presence of proteoglycan-rich neointimal or early neoatherosclerotic plaque

Attenuated: superficial high signal intensity, high back-scatter, likely indicative of lipid-core plaque

Layered: most frequently presenting as superficial high signall intensity with deep low signal intensity often in peri-strut areas

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A homogeneous tissue pattern on OCT imaging is often considered typical of early-onset BMS-ISR

The other three patterns (attenuated, layered and heterogeneous) may represent part of the neoatherosclerotic disease spectrum, which is more commonly seen in DES-ISR

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Four patterns have been reported in both DES-ISR and BMS-ISR

For example, while a homogenous tissue pattern may be considered typical of BMS-ISR, in very late BMS-ISR (>5 years post-stent implantation), a heterogenous tissue pattern has been reported to be more common.

Similarly, in DES-ISR, OCT findings corresponding to neoatherosclerosis become more common with increasing follow-up time post initial stent implantation.

The tissue pattern may also vary along the length of the stent, with some segments showing a typical, healthy neointima and other segments displaying neoatherosclerosis, which may in some cases be complicated (i.e., with plaque rupture)

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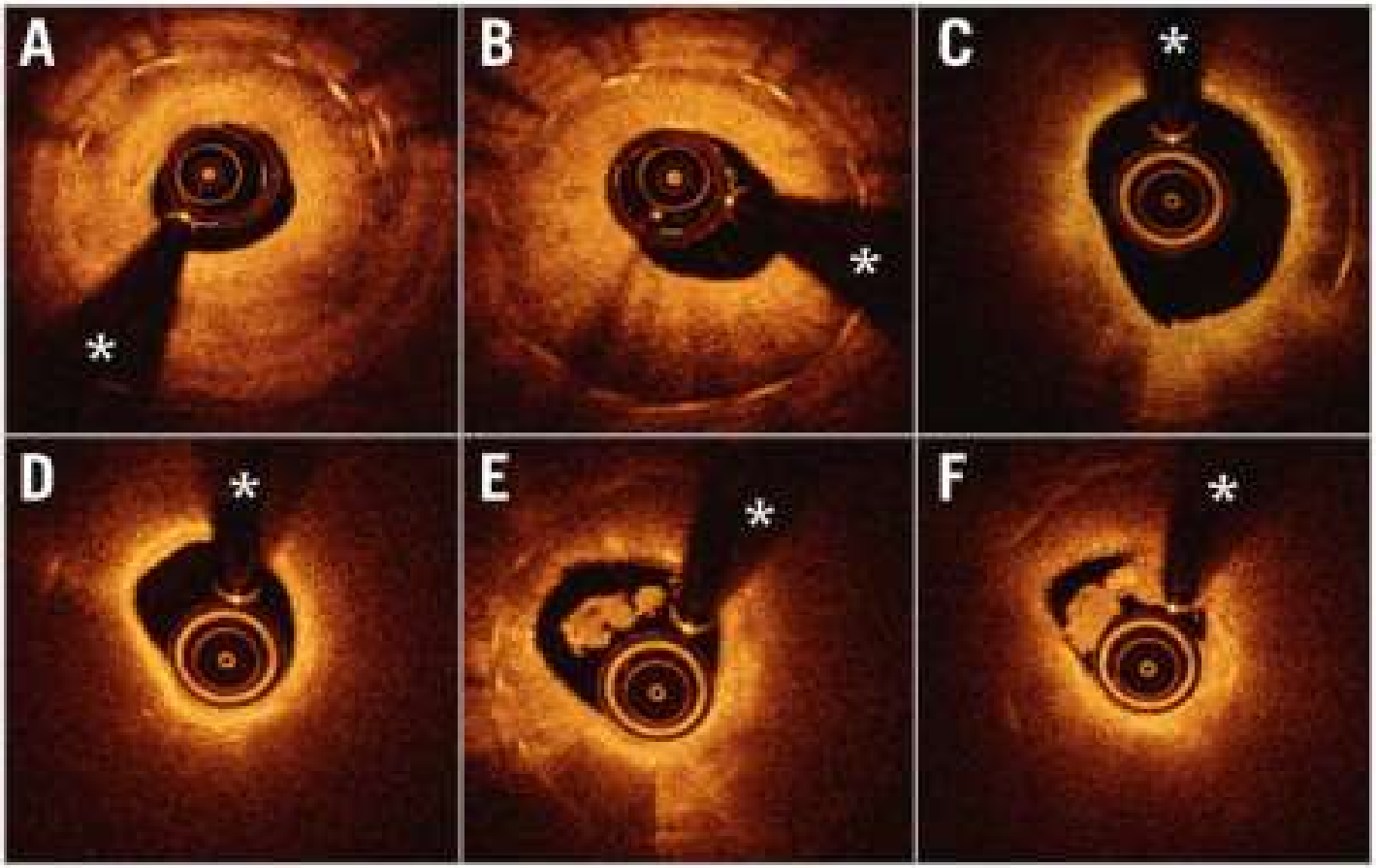

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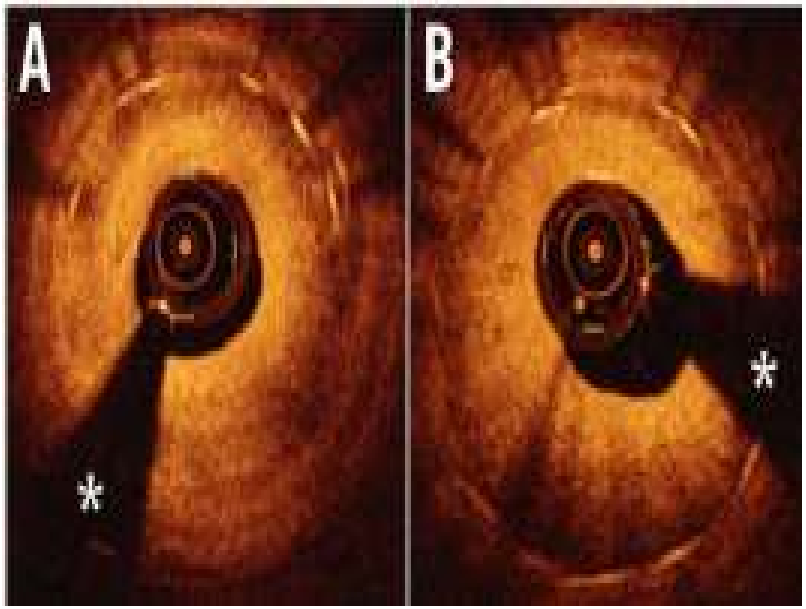
A-B) DEMONSTRATE RELATIVELY **HOMOGENEOUS** *SEVERE NEOINTIMAL PROLIFERATION WITH SOME CONFINED DARKER AREAS CLOSE TO THE UNDERLYING STENT STRUTS THAT ARE READILY VISUALISED (BRIGHT DOTS CASTING A DORSAL SHADOW)*



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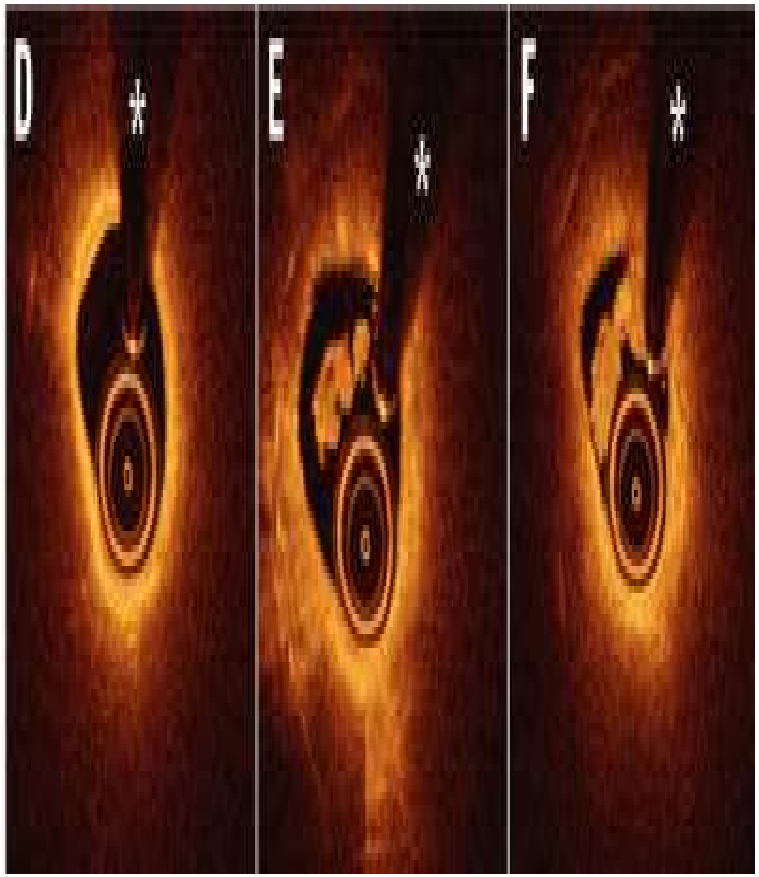
C-F) Typical images of neoatherosclerosis.

In C and D, a bright superficial intima and a large lipid plaque (dark area with diffuse borders) is demonstrated obscuring the underlying stent struts. A potential diagnosis of an intimal layer infiltrated by macrophages should be considered.

In E and F, neoatherosclerosis with intracoronary thrombus is demonstrated.

In E, the bright localised image with dorsal shadow (6-7 o'clock) is suggestive of clusters of macrophages. (denotes wire artefact).*



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CORRELATION BETWEEN IMAGING AND HISTOLOGY

Homogenous tissue appearance on OCT has been shown to correspond to neointima and fibrous connective tissue as a result of smooth muscle cell proliferation.

Heterogenous tissue patterns are associated with increased fibrin depositions and loose connective tissue.

In addition, large lipid pools have been detected in patients showing the typical lipidic pattern characteristic of neoatherosclerosis.

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IVUS

Deeper tissue penetration

No blood-free field

Wavelength of IVUS is ~50 μm

Axial resolution of 150 μm,

Detailed tissue characterisation is not possible.

Demonstrate: neointimal hyperplasia, mature neoatherosclerosis, stent underexpansion, stent undersizing, and vessel calcification.

EEL is usually well delineated, both at the reference segment and beyond the stent struts, allowing accurate vessel sizing.

Virtual histology IVUS has also been used to demonstrate neoatherosclerosis in both BMS-ISR and DES-ISR, although this technology is not widely used in clinical practice at present.

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INTRACORONARY PHYSIOLOGY (FFR OR IFR)

Decision-making for patients with ISR of moderate severity

However, there are limited data on the use of FFR or iFR for the assessment of ISR.

Previously published data with one-year follow-up have suggested that conservative management of angiographically moderate (40-70%) ISR lesions with an FFR value of ≥0.75 is safe.
However, there are no randomised data supporting an FFR-guided ISR treatment strategy. In general, patients with ISR should go through the same diagnostic pathway as patients with *de novo* CAD.

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Achilles heel
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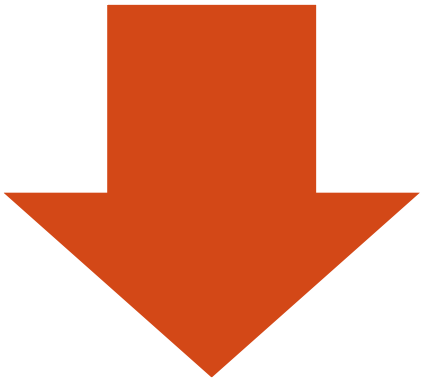
ACUTE GAIN, AND LATE LUMINAL LOSS

Acute gain=MLD(preprocedure) - MLD immediately post-procedure

LLL is defined as the difference between

the MLD immediately post-procedure and the MLD at follow-up angiography.



Minimise LLL.

Maximise acute gain

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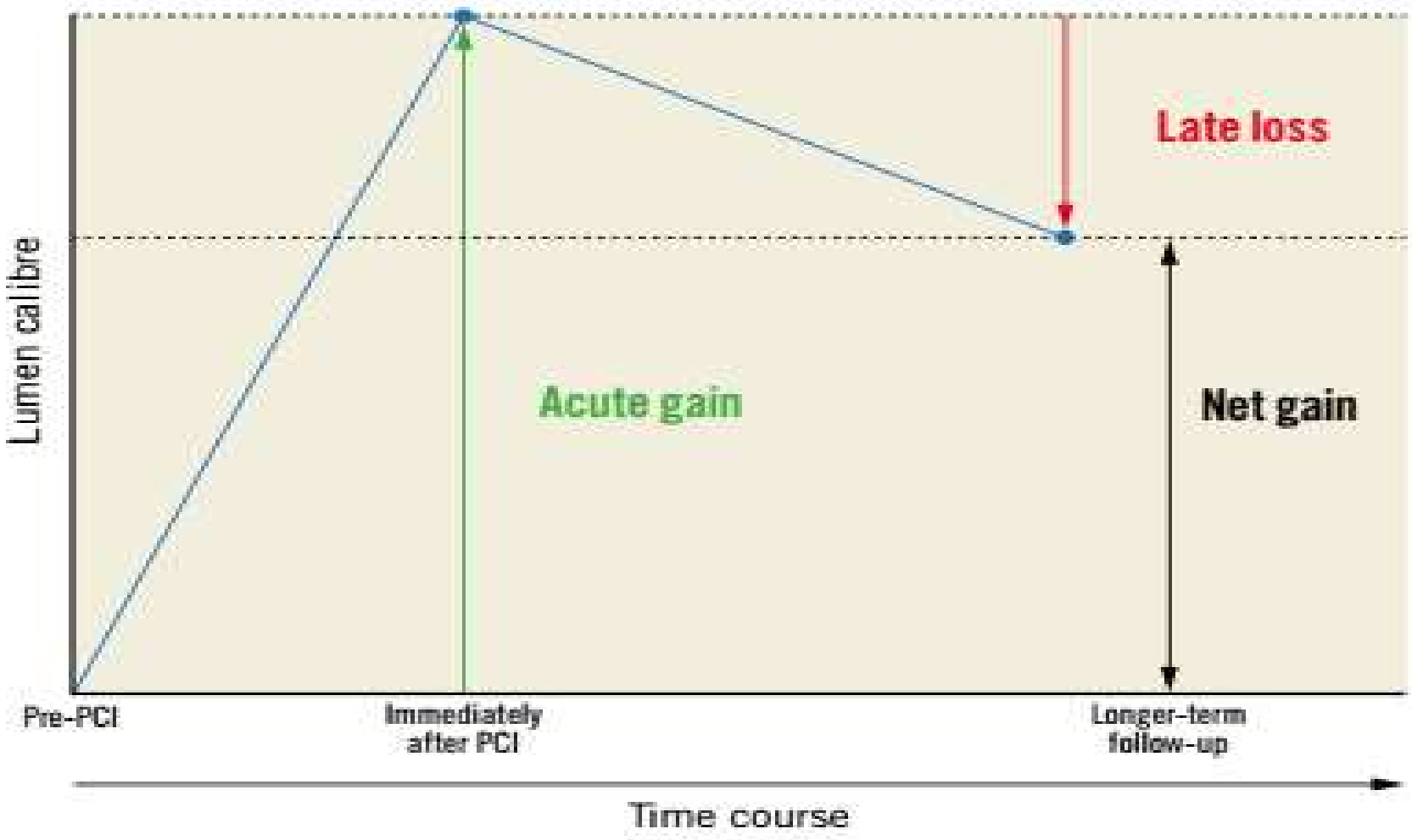
Late loss
Acute gain
Net gain
Lumen calibre
Pre-PCI
Immediately after PCI
Longer-term follow-up
Time course

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DCB therapy is Low acute again and Low late loss

DES PCI High acute gain but also High late loss.

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A significant proportion of ISR lesions are associated with stent underexpansion, which may itself be secondary to vessel calcification.

Indeed, it is noteworthy that in ISR treated with DES, ***primary stent underexpansion*** (i.e., underexpansion of the re-stenosed stent) has been associated with an increased risk of ***secondary stent underexpansion*** (i.e., underexpansion of the second stent used to treat the re-stenosed stent).

This in turn has been associated with an increased risk of MACE and ISR recurrence. Post-procedural stent underexpansion has also been shown to predict recurrence for ISR treated with DCBs.

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Indeed, suboptimal treatment of ISR can result in a vicious cycle, in which the risk of recurrence is increased and subsequent management becomes more and more challenging.

This is of particular concern when patients are treated with an additional DES (the so-called ***"sandwich strategy"***) leading to multiple stent layers or the ***"onion skin phenomenon"***

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THE EVIDENCE BASE FOR THE TREATMENT OF ISR

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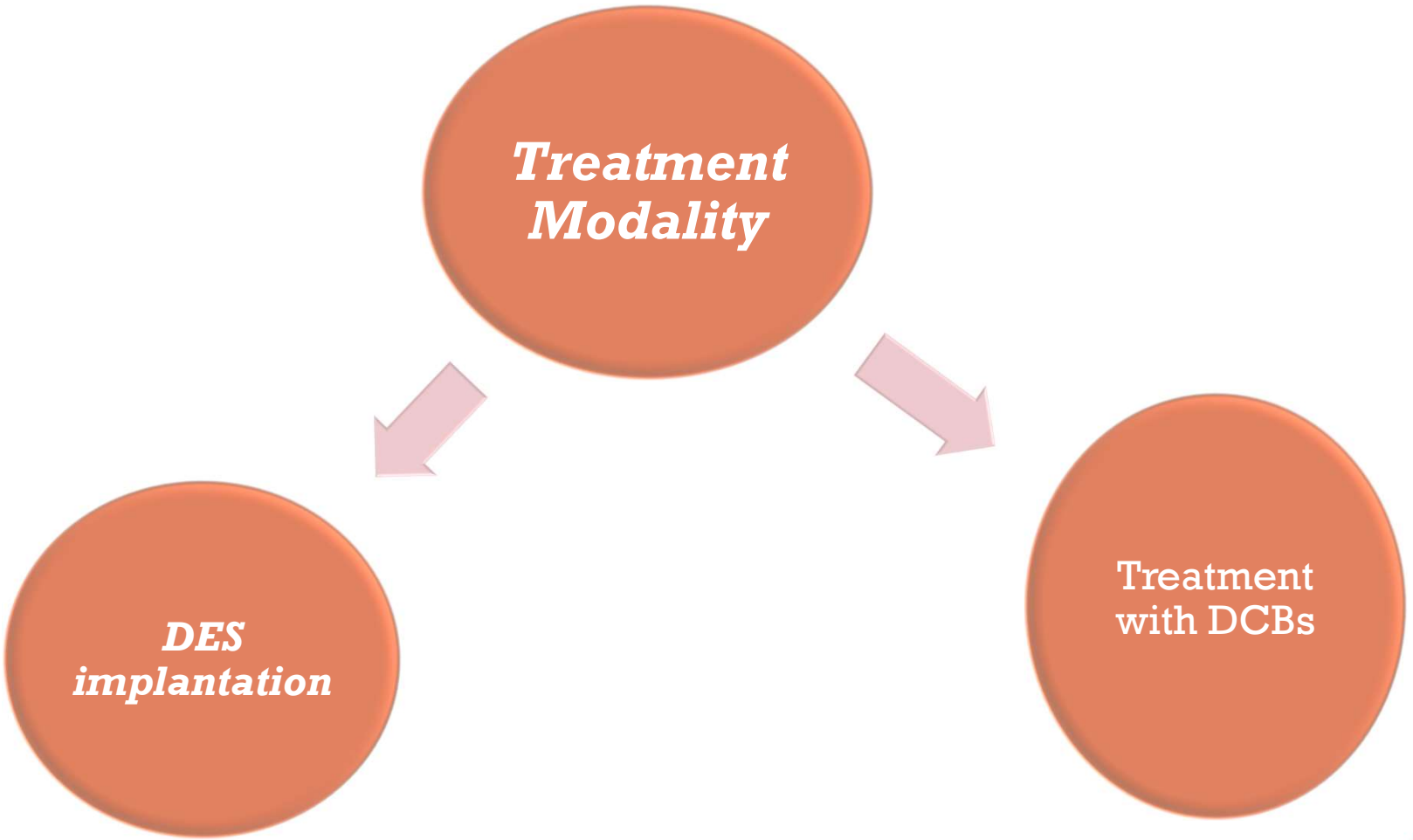

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DRUG-ELUTING STENTS

Meta-analyses have ranked ***DES implantation as the most effective treatment*** for ISR

In addition, head-to-head trials have demonstrated
the superiority of DES implantation to several other therapeutic
modalities for ISR, including BA intravascular brachytherapy (IVBT), and paclitaxel DCBs

Adequate ***lesion preparation*** has been achieved prior to implantation of a new DES
for the treatment of ISR, with particular care taken to tackle any underexpansion of the original stent.

In the case of stent fracture, re-stenting will be required in the majority of cases

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DES STRATEGY: HETERO-DES VS HOMO-DES

It has been hypothesised that treating DES-ISR using a DES with an alternative anti-proliferative agent (the "***hetero-DES" strategy***) might provide superior outcomes to using a DES with the same antiproliferative agent (the "**homo-DES" strategy**).

This hypothesis is based on the concept that drug resistance may have played a role in the development of the initial DES-ISR.

The only randomised trial on this topic, ***ISAR DESIRE-2, did not show*** a benefit to the hetero-DES strategy for the treatment of sirolimus-eluting stent ISR.

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Alternatively, the ***RIBS-III study*** had suggested a

hetero-DES strategy may provide superior outcomes, although this study was not randomized and the alternative treatment decisions were at the discretion of local investigators

A meta-analysis has suggested that there may be a benefit to a hetero-DES strategy but this included results from several observational analyses, limiting the validity of the findings

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DRUG-COATED BALLOONS

DCB catheters are comprised of standard angioplasty balloons and a matrix coating that is applied to the surface of the balloon. The balloon coating is typically comprised of two elements: a lipophilic active drug and a spacer or excipient which increases the solubility of the active drug and facilitates its transfer from the balloon surface to the vessel wall

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DCBs provide anti-proliferative therapy without the requirement for an additional metallic scaffold.

Another stent layer is undesirable (i.e., multiple previous stent layers, the presence of a major side branch)

Mechanism of ISR is stent maldeployment

High bleeding risk

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PACLITAXEL DCBS

RCTs have demonstrated the superiority of DCB therapy to several other treatment modalities for ISR, including BA and BMS implantation

Of note, concern was raised in a 2018 meta-analysis regarding excess mortality associated with paclitaxel-coated balloons and stents in femoropopliteal disease.

However, several subsequent studies have questioned these findings in peripheral arterial disease

Importantly, in the setting of CAD, the use of paclitaxel DCBs has never been linked with safety issues or excesses in mortality.

Further reassuring information in this regard was recently provided by a large meta-analysis

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SIROLIMUS DCBS

Given that network meta-analysis has suggested that ***-limus-eluting DESs*** are associated with ***superior outcomes*** compared to paclitaxel-eluting DESs for the treatment of ISR.

It could be hypothesised that similar advantages might exist when comparing the two DCB technologies for the treatment of ISR.

Until very recently, the technology to ensure adequate binding, persistence and transfer of -limus-based drugs from DCBs to the arterial wall did not exist.

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DCB: THE IMPORTANCE OF LESION PREPARATION

Use ***of cutting or scoring balloons*** to impact on the ISR obstructive tissue prior to DCB treatment may help to ***improve the delivery of the anti-proliferative agent***.

The ***ISARDESIRE 4 trial*** demonstrated that neointimal modification with a scoring balloon improved the anti-restenotic efficacy of DCB therapy.

Interestingly, a drug-coated scoring balloon has been developed, combining both treatment modalities in one device. This has shown promising results in initial studies when compared to an uncoated scoring balloon alone, though it should be acknowledged that the ***sequential use*** of the devices might be the ***most efficacious*** approach

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DES VS DCB FOR THE TREATMENT OF ISR: DIRECT EVIDENCE

Despite the theoretical advantages of DCBs in the management of ISR, a meta-analysis of randomised controlled data comparing DES versus paclitaxel-DCB angioplasty has demonstrated that repeat DES implantation for ISR is moderately more effective in reducing the rate of TLR at 3 years

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In this setting, repeat ***DES implantation*** provides **better acute angiographic results** than DCB treatment, including increases in the MLD and reductions in residual %DS.

In most head-to-head RCTs, these superior acute angiographic results with DES as compared with DCB treatments are ***maintained at longer-term follow-up***

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The DAEDALUS study, a meta-analysis of patient-level data from 10 RCTs which included 1,976 patients, demonstrated that DESs reduced the need for subsequent TLR(Target Lesion Revascularization) compared with paclitaxel DCBs at 3 years.

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ADJUNCTIVE THERAPEUTIC MODALITIES FOR ISR

1- **BALLOON ANGIOPLASTY**

2- **CUTTING/SCORING BALLOONS**

3- **INTRAVASCULAR BRACHYTHERAPY**

4- **ABLATIVE STRATEGIES:**

   a- EXCIMER LASER CORONARY ATHERECTOMY

   b- **ROTATIONAL ATHERECTOMY**

5- **INTRAVASCULAR LITHOTRIPSY(IVL)**

6- **BIORESORBABLE VASCULAR SCAFFOLDS**

7- **CORONARY ARTERY BYPASS GRAFTING**

8- **ADJUNCTIVE MEDICAL THERAPY**

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BALLOON ANGIOPLASTY

Acute Gain: Tissue extrusion (both longitudinal and axial) in addition to stent expansion(But short lived) re-intrusion occurring shortly after the last balloon inflation.

This strategy is plagued by recurrent severe tissue proliferation and has been virtually abandoned in Europe as a definitive therapy.

In the US, where DCBs have still not been approved, isolated conventional BA is still used for cases with focal ISR where the risk of recurrence is deemed to be low.

In the setting of an underdeployed stent, non-compliant or ultra-high-pressure noncompliant balloons (UHPNCBs) at high pressures should be used to improve stent expansion.

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BALLOON ANGIOPLASTY

However, based on current data,

A-Isolated BA is not routinely recommended

B- For lesion preparation

C-Final optimisation of DES implantation.

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CUTTING/SCORING BALLOONS

Cutting balloons are comprised of standard balloon catheters mounted with lateral metallic blades, which on inflation of the balloon incise into the treated stenotic plaque.

Scoring balloons have a broadly similar mechanistic basis but employ low-profile nitinol wires (of the order of 125 µm) on the surface of the balloon catheter in a spiral formation

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CUTTING/SCORING BALLOONS

The two main advantages to their use are that the incision of the blades into the stenotic plaque may favour subsequent tissue extrusion and the interaction of the blades with the plaque serves to anchor the balloon in the plaque. Both cutting and scoring balloons may play a valuable role in lesion preparation prior to DESs or DCBs in the treatment of ISR.

However, as a standalone treatment, both technologies are hindered by their inability to inhibit neointimal proliferation and suffer from similar limitations to BA.

In the ISAR-DESIRE 4 trial, the use of a scoring balloon prior to a DCB has been shown to improve the anti-restenotic efficacy of the DCB.

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CUTTING/SCORING BALLOONS

Cutting/scoring balloons may also be useful to avoid the "watermelon seeding" phenomenon that can occur when dilating ISR lesions, particularly in the presence of severe or diffuse patterns of ISR.

"Watermelon seeding" is associated with prolonged procedure times, suboptimal acute angiographic results and inferior long-term outcomes. It can result in ***"geographic miss"***, which can subsequently lead to recurrent edge-ISR.

A non-slip element balloon has also shown similar efficacy to high-pressure non-compliant balloons in lesion preparation pre-DCB treatment for ISR.

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INTRAVASCULAR BRACHYTHERAPY

The aim of this treatment modality is to impede neointimal cell growth within the target area without damage to the surrounding tissue. The radiation achieves this effect via two primary methods: direct damage secondary to ionising emissions and injury secondary to free radical generation.

Several randomised clinical trials demonstrated that IVBT was superior to the mechanical alternatives available at the time.

When DESs became available, they rapidly superseded IVBT due to both their greater simplicity and superior results in the setting of BMS-ISR.

However, there are no randomised data on the use of IVBT in the setting of DES-ISR. Observational analysis has suggested that ***IVBT may have a role in recurrent ISR.***

This lack of evidence has prevented the common use of this technology in modern practice, where IVBT has been abandoned in most centres.

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ABLATIVE STRATEGIES

1- EXCIMER LASER CORONARY ATHERECTOMY(ELCA)

2- ROTATIONAL ATHERECTOMY

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EXCIMER LASER CORONARY ATHERECTOMY

ELCA is a debulking technique which uses ultraviolet spectrum wavelengths to ablate tissue.

It does this by generating heat and shockwaves. Despite some early historical studies demonstrating the safety and feasibility of this technique, there are limited recent data to support the systematic use of ELCA as the primary treatment for ISR and no randomised data are available on the use of ELCA for DES-ISR.

However, in selected cases it may have an adjunctive role for lesion preparation, particularly ***for recurrent ISR in the setting of severe calcification***.

For the rarely encountered patients with undilatable ISR as the result of severely underexpanded stents due to a heavily calcified arterial wall, this technique may facilitate stent expansion, particularly if contrast is injected to induce further barotrauma and microcavitation.

Evidence in this regard stems only from small observational series but it nevertheless remains a ***useful option as a bailout strategy*** when other therapeutic strategies have failed.

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ROTATIONAL ATHERECTOMY

RA is another ablative technique which can be used to debulk ISR lesions and facilitate the application of subsequent treatments (as part of a combined strategy).

There are historical RCTs comparing RA to BA in BMS-ISR. While the ROSTER trial (that mandated the use of IVUS during the intervention) suggested superior results with RA compared to BA, the much larger ***ARTIST trial reported inferior results*** with RA and a higher number of procedural-related complications.

However, it should be noted that this may have been related to the trial protocol, which mandated **lower balloon inflation pressures** in the RA arm of this study, and to ***the lack of systematic IVUS use*** to rule out severe underexpansion.

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ROTATIONAL ATHERECTOMY

There are no randomised data for the use of RA in the treatment of DES-ISR.

Role in:

A- Lesion preparation prior to DCB application

B- Recurrent DES implantation.

It should be considered a high-risk procedure and particular care must be taken to avoid burr entrapment within the ISR lesion.

The successful use of RA to ablate metal ("stentablation"/"rotastenting") in the exceedingly rare cases of severely underexpanded and undilatable stents has also been reported.

However, this procedure has obvious inherent potential risks (burr entrapment, vessel perforation), and indications for its use are likely to be extremely restricted, given that more attractive and safer strategies are now available to tackle this unique problem.

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INTRAVASCULAR LITHOTRIPSY

Intravascular lithotripsy (IVL) is a relatively new technology which uses localised pulsatile sound waves to circumferentially modify vascular calcium.

IVL has been demonstrated to be safe and effective in *de novo* CAD. The use of IVL to facilitate stent expansion in ISR has been described but there are limited data available on this technique and it is regarded as an off-label use.

However, many observational reports have demonstrated that IVL may be used with success in patients with ***undilatable ISR resistant to conventional strategies***, especially in Stent underexpansion due to circumferential coronary artery calcification.

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IVL

In a manner similar to ELCA, the energy produced modifies the compliance of the calcified plaque causing fractures beyond or within the stent.

Compared with ELCA and RA, the use of IVL in patients with ISR is:

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BARE METAL STENTS

BMS implantation was used after BA for the treatment of BMSISR and showed some promise in terms of acute luminal gain compared to BA.

However, in the RIBS-I trial, BMS implantation failed to show an advantage at 6-month follow-up in comparison to BA for the treatment of BMS-ISR.

In that study, BMSs were superior to conventional BA only in the predefined subset of patients with large (≥3 mm) vessels.

BMSs also proved to be superior to BA in patients presenting with edge-ISR.

There are no trials assessing the value of BMSs for the treatment of DES-ISR andas such, ***their role in the management of ISR is largely historical.***

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BIORESORBABLE VASCULAR SCAFFOLDS

Bioresorbable vascular scaffolds (BVS) were considered potentially attractive for the treatment of ISR.

However, the use of BVS for patients with ISR was associated with a higher TLR rate in comparison to results obtained with DESs in previous studies.
Polymeric BVS are no longer commercially available.

The potential value of magnesium-based BVS (Mg-BVS) has been investigated in some early preliminary studies. but further research is required to determine whether they will play a future role in the treatment of patients with ISR

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MANAGEMENT OF PATIENTS WITH BVS-ISR

The ***RIBS VII study*** prospectively registered the treatment of patients with BVS-ISR.

Overall and after adjusting for potential confounders, patients with BVS-ISR had

similar clinical outcomes to patients with restenosis of metallic stents.

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CORONARY ARTERY BYPASS GRAFTING

No RCTs comparing CABG to other treatment modalities for ISR.

However, some observational analyses have reported that patients treated with CABG for ISR (85% of whom had multivessel disease) had superior outcomes compared to percutaneous therapies.

CABG considered in patients with

(1) ISR of the left main stem (LMS)

(2) Recalcitrant ISR in a major vessel

(3) Associated multivessel disease

(4) ISR located in the ostial LAD

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ADJUNCTIVE MEDICAL THERAPY

The use of several adjunctive anti-inflammatory or anti-proliferative medications has been suggested for patients with ISR, in particular for patients presenting with recurrent ISR.

It was hypothesised that the use of adjunctive medical therapies would reduce the risk of ISR recurrence.

In the ***OSIRIS study***, oral sirolimus resulted in a significant improvement in 6-month angiographic parameters. However, this early benefit was attenuated at longer follow-up and concern regarding potential side effects led to reduced interest in this therapy.

Currently there is no clear evidence supporting the use of adjunctive systemic anti-proliferative medical treatments in these patients.

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SPECIFIC CLINICAL SCENARIOS

RECURRENT ISR

Recurrent ISR refers to ISR that has recurred after the initial treatment of ISR.

If the ISR was initially treated with repeat implantation of a stent, this means that the recurrent ISR lesion will have two stent layers.

Some ISR lesions may have more than two stent layers. These cases appear to be systematically associated with underexpansion of the initial stent.

ISR-PCI with a DCB has been associated with worse outcomes for patients with three layers of stent than for those with one or two stent layers.

Therefore, it may be advisable to avoid a third layer of stent when treating recurrent ISR, although DES implantation has been reported to be safe and effective in recurrent ISR with two stent layers.

Another study reported that ***DES implantation was superior to BA in patients with recurrent ISR previously treated with a DES.***

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RECURRENT ISR

However, there are limited dedicated randomised data available to guide treatment decisions in this challenging lesion subset.

IVBT has been reported to be a useful modality for recurrent ISR with multiple stent layers but a meta-analysis suggests that TVR still occurs in approximately 1in 4 patients at 2 years in this setting.

DCBs may also be useful in this challenging setting although the 1-year TLR incidence was reported as

14.5% in the 1-stent layer group

14.9% in the 2-stent layer group

41.2% in the 3-stent layer group

in a study by Yabushita et al.

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RECURRENT ISR

When managing recurrent ISR, it is particularly important to determine if there are persistent mechanical issues which were not adequately addressed during the initial ISR therapeutic procedure, and which may have contributed to the ISR recurrence.

Failure to deal with these persistent mechanical issues will likely increase the risk of future TLR.

In most cases underexpanded stents appear to represent the trigger for recurrence, although localised stent fractures (i.e., at hinge points) may also contribute to recurrence in some cases.

Ensuring optimal final stent expansion is of paramount importance in this scenario.

Whether the systematic use of IVL in these patients will help to improve clinical results in patients with recurrent ISR remains to be determined

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CABG considered in patients with recurrent ISR affecting:

LMS

Ostial LAD

Multivessel disease

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ISR IN THE SETTING OF SEVERE CALCIFICATION AND STENT UNDEREXPANSION

Coronary artery calcification is a recognised major risk factor for ISR.

For ISR in the setting of calcification and stent underexpansion, calcium modification may be required. RA, ELCA, IVL and UHPNCBs can all be used to modify calcium and facilitate stent expansion in this setting.

Repeat IVI following calcium modification may be useful to ensure it has been successful, particularly if definitive therapy with DES implantation is planned.

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LEFT MAIN STEM ISR

There are limited data on the management of LMS ISR.

The FAILS study reported that LMS ISR could be managed percutaneously in the majority of cases.

A retrospective analysis has also suggested that DES and DCB treatments can provide similar outcomes in this setting.

However, a high mortality after TLR for LMS stent failure has been reported, and ***CABG*** should be considered in suitable patients.

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ISR-CTO

ISR-CTO was suggested to represent its own distinct class of ISR in the Mehran classification.

ISR-CTO PCI has been associated with a higher risk of complications and adverse events during follow-up in comparison to CTO-PCI in some reports. However, other studies have reported comparable results to *de novo* CTO-PCI.

Visualisation of the stent in different projections during the ISR-CTO PCI procedure provides a roadmap that may facilitate advancement of special wires within the true lumen.

Procedural outcomes may be impacted by operator experience and ISRCTO PCI should be regarded as a highly specialised, high-risk procedure.

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STENT FRACTURE

Stent fracture may be identified in association with ISR and is generally defined as ***complete or incomplete separation of the stent strut on angiography*** and/or the absence of a stent strut on at least one slice on IVUS.

For ISR lesions secondary to stent fracture, ***repeat stenting*** will be required in the majority of cases, although it must be acknowledged that there is an absence of highquality, randomised data to support this recommendation.

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ISR TREATMENT ALGORITHM

we would recommend the ***use of IVI*** for all ISR cases

StentBoost may also be useful in particular to identify mechanical issues like stent fracture and stent underexpansion

Repeat IVI to ensure mechanical prior to definitive therapy

If IVI is not available, operators should focus on adequately predilating the ISR lesion and optimising stent expansion. This may include the use of non-compliant(NC) balloons and UHPNCBs.

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Cutting/scoring balloons can also be useful and should be used prior to DCB therapy where possible in order to optimise DCB efficacy.

DES used preferentially in:

Significant dissections

Persistent residual stenosis >40%

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Similarly, if the ***underlying stent type is not known***, operators should favour DESs given that they have been shown to be moderately more effective than DCB therapy overall for the management of ISR.

However, operators need to balance this moderate efficacy benefit against the implantation of another stent layer

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Given that DCB and DES implantation have comparable outcomes in BMS-ISR,

DCB may be preferable in the first instance.

In patients with high bleeding risk, the use of DCBs may also facilitate a more abbreviated duration of DAPT

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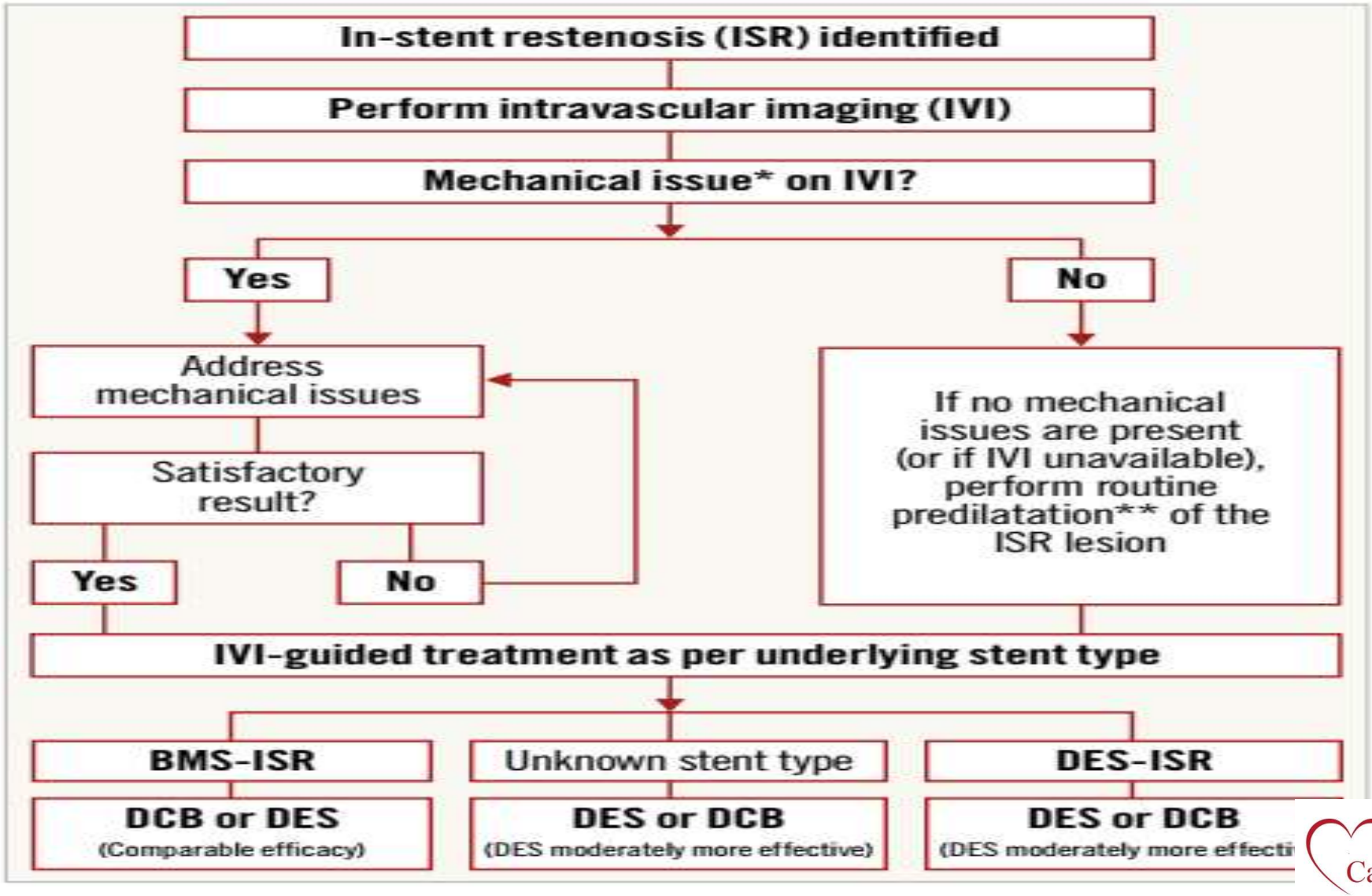
In-stent restenosis (ISR) identified
Perform intravascular imaging (IVI)
Mechanical issue* on IVI?
Yes
No
Address mechanical issues
Satisfactory result?
Yes
No
If no mechanical issues are present (or if IVI unavailable), perform routine predilatation** of the ISR lesion
IVI-guided treatment as per underlying stent type
BMS-ISR
Unknown stent type
DES-ISR
DCB or DES
(Comparable efficacy)
DES or DCB
(DES moderately more effective)
DES or DCB
(DES moderately more effecti

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Mechanical issues

Stent undersizing

Stent underexpansion

Vessel calcification

Stent fracture

Geographic miss

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Mechanical issues can be addressed via a variety of methods

BA

RA

ELCA

IVL

UHPNCB

Cutting, and scoring balloons

Predilatation can be performed with BA, UHPNCB, cutting, or scoring balloons.
Cutting and scoring balloons may be particularly useful prior to planned DCB therapy

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FUTURE INTERVENTIONAL PARADIGMS

Heterogenous ISR on OCT DESs showed an advantage over DCBs. No such advantage was seen in patients with a homogenous pattern on OCT.

Indeed, this hypothesis will be examined by the ***upcoming ISAR-DESIRE 5 trial***, an RCT with a factorial design randomising patients with homogenous and heterogenous ISR tissue patterns on OCT to either DCB or DES treatment.

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OPTIMAL FOLLOW-UP AND TREATMENT AFTER ISR-PCI

ISR is recognised as being challenging to treat, with high rates of recurrence at medium- to long-term follow-up ***Routine control angiography after ISR-PCI*** is one potential strategy to identify recurrent restenosis, although this approach has not been assessed in RCTs and might lead to an increase in the number of repeated revascularisations without clinical indication.

However, in the absence of RCT evidence, follow-up after ISRPCI should primarily consist of clinical follow-up aimed at identifying signs or symptoms of recurrent ischaemia, which could be suggestive of ISR recurrence.

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DAPT DURATION AFTER ISR-PCI

Currently, there is insufficient evidence to suggest that patients undergoing PCI for ISR require a different DAPT composition and duration to patients undergoing PCI for *de novo* lesions.

In general, DAPT composition (i.e., the use of conventional or more potent P2Y12 inhibitors) and duration should be guided by the clinical presentation of patients with ISR.

Of note, patients treated with DCB will, in general, require a shorter duration of DAPT in comparison to patients treated with DES.

However, it is also important to recognise that currently there is insufficient evidence that DAPT composition and duration should be guided by the type of PCI (DCB or DES) for ISR.

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A subanalysis of the ***PRODIGY trial*** has suggested that a prolonged DAPT regimen (24 months) may be beneficial for patients undergoing ISR-PCI compared to an abbreviated DAPT regimen (6 months), although this requires confirmation in larger, dedicated trials.

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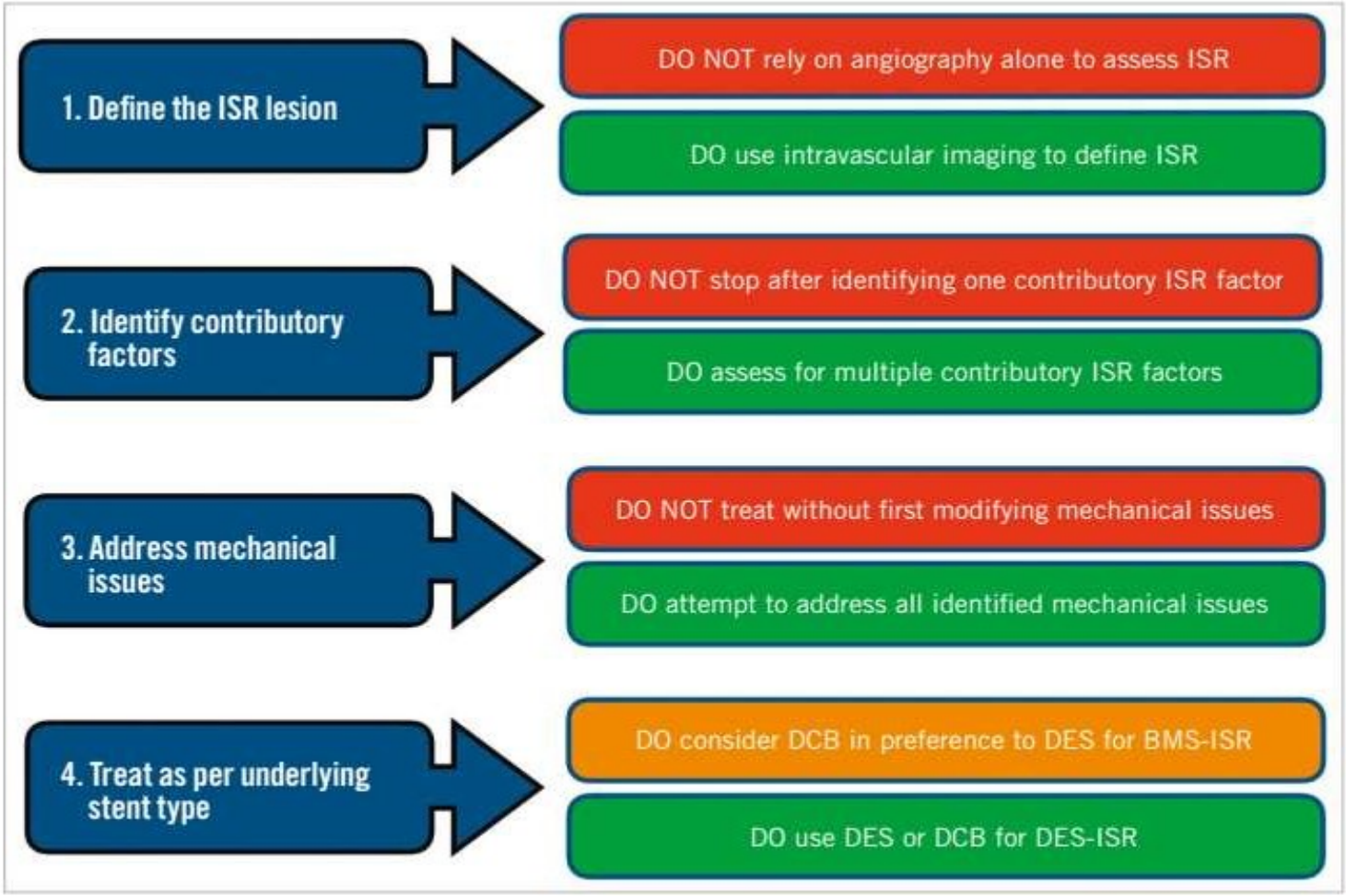

Figure 9. *Do's and Don'ts of ISR-PCI. BMS: bare metal stent; DCB: drug-coated balloon; DES: drug-eluting stent; ISR: in-st PCI: percutaneous coronary intervention*

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CONCLUSIONS

Despite recent advances in PCI, ISR remains a significant issue and the most common cause of stent failure, accounting for 5-10% of all PCI procedures in modern clinical practice.
While the relative rate of ISR has been reduced with newer-generation DESs in comparison to the BMS era, increasing procedural volume and complexity has resulted in a higher absolute number of ISR-PCI procedures being performed in modern practice.
Current evidence suggests that DESs or DCBs are the optimal treatment modalities for the majority of ISR cases.
IVI can provide useful information to guide treatment decisions in ISR-PCI, and future ISR interventional paradigms may be guided by IVI ISR tissue patterns.

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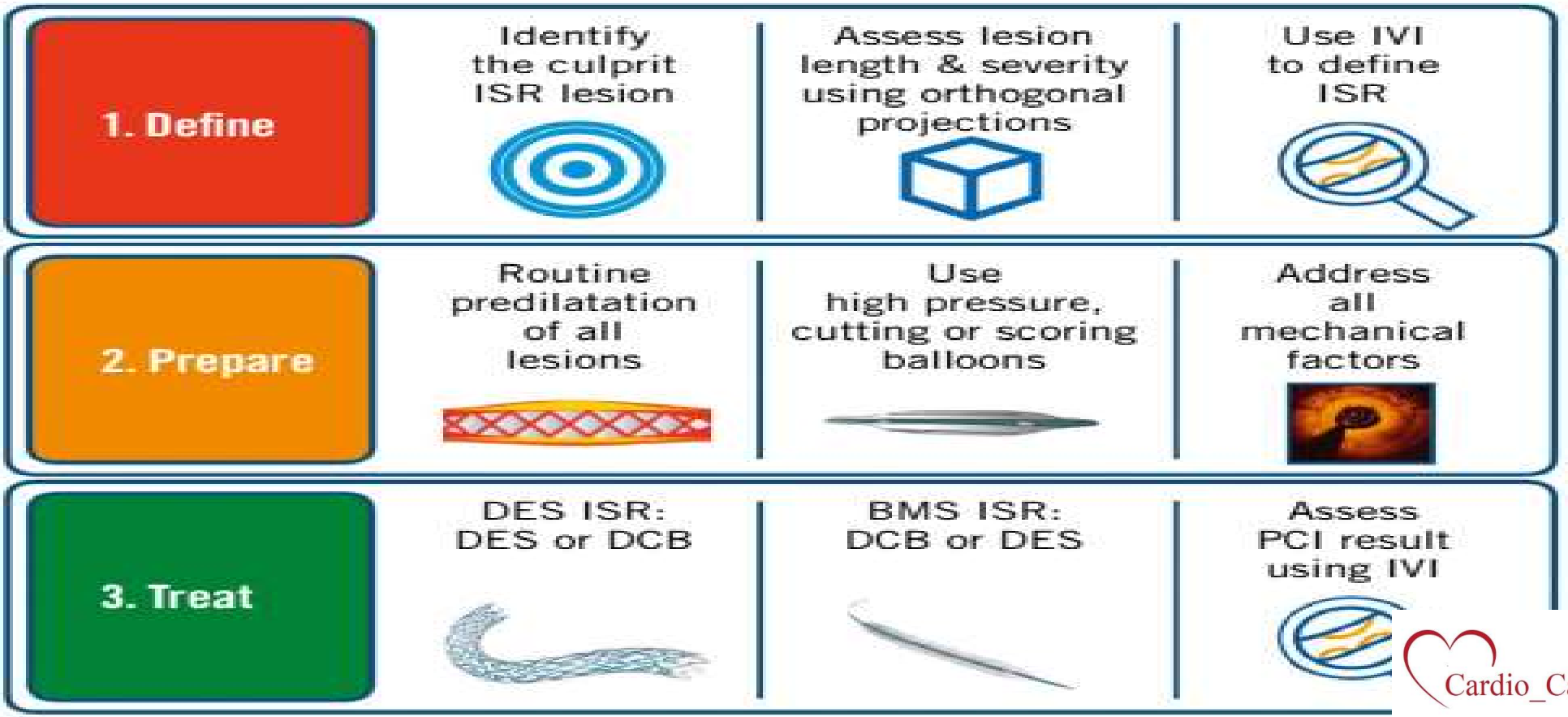
A SUMMARY OF THE MAJOR PRINCIPLES OF MANAGING ISR



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